Controller in the cell

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Quality control is important – this is not only applicable to industrial production but also true for all life processes. However, whereas an enterprise can start a large-scale recall in case of any doubt, defects in the quality control systems of cells are often fatal. This is seen in particular in neurodegenerative diseases such as Alzheimer's, Parkinson's, or amyotrophic lateral sclerosis (ALS), in which fundamental mechanisms of cellular quality control fail.

A Frankfurt research team led by Ivan Dikic, Professor for Biochemistry, now successfully decoded molecular details enabling a better understanding of two neurodegenerative diseases. Their work focuses on "autophagy" as a central element of cellular quality control. Autophagy literally means "self-eating," and refers to a sophisticated system in which cellular waste is specifically detected, surrounded by membranes, and removed. Typical targets are harmful or superfluous proteins or cell organelles, even pathogens such as bacteria or viruses can be eliminated via this pathway.

Together with colleagues from Jena, Aachen, and the Netherlands, the team of Ivan Dikic has now identified a new autophagy receptor, the so-called FAM134B protein. In the online issue of the renowned journal *Nature*, the researchers report a new function of FAM134B in the constant renewal of the endoplasmic reticulum (ER), an important cell organelle. FAM134B ensures proper breakdown and disposal of dysfunctional ER.

"Too little FAM134B leads to an uncontrolled dilation and expansion of

this organelle, which is harmful for the cell," explains Ivan Dikic. "The discovery of FAM134B as a new autophagy receptor is already a milestone. Even more exciting is the connection to a rare neuronal hereditary disease." Collaborators from the Human Genetics Department at the University Hospital of Jena, PD Ingo Kurth and Professor Christian Hübner, already demonstrated in 2009 that mutations in FAM134B cause the death of sensory neurons in a disorder called hereditary sensory and autonomic neuropathy type II (HSAN II). The exact function of FAM134B, however, remained unknown until now.

HSAN II is a very rare hereditary disease in which both pain and temperature sensitivity and perspiration are impaired. For example, affected patients burn and hurt themselves easily, because they cannot feel heat and pain signals. Mutation of FAM134B in a mouse model leads to a similar syndrome "The mutated protein cannot function as a receptor. With these discoveries we have taken a big step to understanding the molecular causes of this neuropathy. At the same time, the importance of autophagy in cellular quality control is underlined," explains Dikic.

His laboratories at the Institute for Biochemistry II (IBC II) and at the Buchmann Institute for Molecular Life Sciences (BMLS) recently participated in another groundbreaking study of a neurodegenerative disease, ALS. Typically, ALS leads to death after three to four years due to the massive loss of motor neurons ALS (Amyotrophic lateral sclerosis) is a devastating disease characterized by loss of motor neurons and neurodegeneration, usually leading to death within 3-4 years. Despite being classified as rare disease, public awareness is very high, fueled by celebrity patients like Stephen Hawking and culminating in last years' Ice Bucket Challenge, the first charity campaign with global impact. Still, there is no treatment for ALS, despite intensive research in the field.

As reported in the title story of *Nature Neuroscience*'s May issue, an

international team has now progressed significantly in understanding gene defects responsible for ALS. The scientists discovered that mutations in a specific enzyme, Tank-binding kinase (TBK1), occur more frequently in families with ALS. The Dikic lab was particularly involved in clarifying the function of TBK1 and was able to show that the mutations found in patients interrupt the interaction of TBK1 with the autophagy receptor optineurin. Optineurin is involved, for example, in the elimination of aggregated proteins and bacterial infection defense. Co-lead author Dr. Benjamin Richter comments: "For me as a medical doctor working in basic science, this story represents the ideal case of explaining the pathophysiology of a disease by a collaborative effort across disciplines."

"The two studies show in an unparalleled way how general concepts can be developed from individual findings," emphasizes Ivan Dikic. When cellular quality control in neurons fails over a long time, the consequences for the overall organism are disastrous. "Autophagy has crystalized as a common central mechanism of cellular quality control in neurodegenerative disease," says Dikic.

More information: "Regulation of endoplasmic reticulum turnover by selective autophagy." *Nature*, DOI: 10.1038/nature14498

"Haploinsufficiency of TBK1 causes familial ALS and fronto-temporal dementia" *Nature Neuroscience*, Volume:18, Pages: 631–636 Year published: (2015), DOI: 10.1038/nn.4000

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